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On Primary Cholostatic Cirrhosis of the Liver

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History

Physicians have long recognized in "hardening of the liver", the end stage of chronic liver disease. Descriptions of the shrunken and wrinkled organ were given by *Vesalius* and *Morgagni*. The nodules observed by them on the liver were considered to be "tubercules". *Payne* has reproduced a drawing of a cirrhotic liver from the work of *John Browne* in 1685. In this case the ascites was ascribed to excessive drinking of water. In 1793, *Matthew Baillie* differentiated what later became known as cirrhosis from tumors of the liver. He also noted the marked frequency with which the disease occurred in users of alcoholic beverages, a relationship which had already been observed by earlier writers.

The designation "cirrhosis" was proposed by *R. T. H. Laennec*, derived from the Greek work "kirrhos" meaning yellow. The color yellow represented the fatty degeneration or the icteric color of the livers of this disease. Later, it was recognized that the yellow color was insignificant and not at all a frequent accompaniment of liver cirrhosis. More value was placed upon the connective tissue proliferation, the associated contraction and the increased consistency of the liver. Authors tried to change hte name, but the adopted word, "cirrhosis", remained. Indeed, one even designated alterations in other organs (pancreas, lungs, etc.), which showed proliferation of connective tissue with increased consistency, as cirrhosis, even though no sign of yellow color was present.

The similarity of the words "cirrhosis" and "scirrhus" has been a natural cause of confusion between them. To most physicians "cirrhosis" has come to mean "hardening" of the liver and its original use, to designate a color, has been disregarded.

Rokitansky introduced the concept that cirrhosis followed chronic inflammation. Clinicians such as *Frerichs*, followed this thought by suggesting that the disease existed in two stages: the first, one of inflammation and new connective tissue formation, the second, one of contraction and nodule formation. In this early period, cirrhosis by intrahepatic and extrahepatic obstruction was not distinguished.

Charcot and *Gombault* in 1876, were the first to show, by ligating the common duct of animals, that cirrhosis of the liver may develop from disturbances of bile flow or, in other words, from a bile stasis. Development of xanthomas of the skin as an accompaniment of bile stasis, was first reported by *T. Addison* and *W. Gull*, in their publication of 1851, entitled "On A Certain Affection Of The Skin, Vitiligoidea Plana And Tuberosa". They reported five cases of a skin affection with which they were not familiar and owing to a certain resemblance between it and the disease described by *Willan* as vitiligo, they suggested the name vitiligoidea. They distinguished two varieties of the affection: the flat, to which they gave the name vitiligoidea plana, and the nodular, which they named vitiligoidea tuberosa. Of the five cases, three were patients with chronic jaundice.

Murchison presented a case published in 1869, of a 41 year old man who had chronic jaundice and developed multiple xanthomas. Partial occlusion of the bile ducts from the pressure of enlarged glands in the fissure of the liver was believed to be the cause of the chronic jaundice.

C. H. Fagge, reported a case published in 1873, of a patient having had jaundice for seven years before death. Xanthelasma and multiple xanthomas on the extremities and other body areas were present. It was pointed out that xanthelasma could present itself without the presence of hepatic disease as evidenced by a paper reporting thirty-six such cases. Multiple xanthomas appeared to arise only in protracted cases of jaundice. *C. H. Fagge* wrote: "The jaundice is peculiar in being very chronic and persistent, lasting for months or even years and although very decided in its hue, in being independent of any obstruction of the hepatic duct, bile being always found in sufficient quantity in the alvine evacuations. The enlargement of the liver is distinguished by being great and uniform, and by its surface being firm, smooth and somewhat tender." On microscopic examination of the liver (after autopsy), the greater portion of connective tissue proliferation was found to be present in the portal canals and between the lobules.

P. H. Pye-Smith in the same year (1873), wrote of a 49 year old woman who through a gallbladder stone (found at autopsy), became jaundiced and developed xanthelasma and xanthomas on the creasing surfaces of the hands and fingers.

W. Moxon, also in 1873, reported a case of chronic jaundice with development of xanthoma in various areas of the body. At autopsy the hepatic duct was found to be bent and obstructed to such an extent that a fine probe would pass through only with care and with some force.

In 1882 *J. Hutchinson*, *A. Sangster* and *H. Radcliffe Croche*, concluded in their presentation and discussion of cases with xanthomatous affections, that at least four fifths of the cases of multiple xanthomas, commencing after puberty, are accompanied by chronic jaundice due to obstruction of the bile ducts. A table of 23 cases of multiple xanthomas in adults all of which had chronic jaundice was given.

Biliary cirrhosis with and without cholelithiasis, was presented by *F. P. Weber* in 1902. He believed that the cirrhosis without the presence of gallstones and without obstruction of the common bile duct was due to: (1) chronic or subacute cholangitis and possibly temporary attacks of chronic cholangitis; (2) obstruction to the outflow of bile. In the cases which he reported, however, the obstruction must have been in the minute bile ducts and was probably due to cholangitis. This afforded an explanation for the remissions and exacerbations of the jandice and other symptoms presented by the disease.

In the year 1905, *T. B. Futcher* presented three cases, all females. Their respective ages were 39, 39 and 42 years. The duration of jaundice, before the xanthomas appeared, was 8 months, 8 years and 1½ years. The cause of the jaundice was gallstones of the common bile duct in two cases, one of which also had a biliary hypertrophic cirrhosis of the liver, and the third case had only a hypertrophic cirrhosis. In case one, there was a spontaneous, complete disappearance of the xanthomas 4½ years after their onset and approximately 4 years after the gallstones were removed at operation. Four fifths of the cases of multiple xanthomas in adults were accompanied by chronic jaundice.

F. Schaaf, in 1938, produced xanthomas in laboratory animals. He maintained that a disturbance in lipoid metabolism, caused by a loss of a particular liver function (regulation of the concentrations of fat emulsifying agents), is of decisive significance. As a result of this there is an impairment of the colloid dispersion of fats in the blood serum, which increases the tendency of the fats to be thrown out of emulsion. Depending upon the degree of impairment of dispersion, xanthomas are formed either with or without local colloid chemical contributory factors (in the former instance there may be only local xanthomas; in the second instance more probably generalized or multiple xanthomas).

The possibility was considered that this functional disturbance of the liver may be preceded by an impaired lipoid excretion. Moreover, there exists the possibility that the formation of xanthomatous skin changes may be facilitated by a characteristic disturbance in lecithin metabolism. It was showned that the metabolic disturbances, as determined by analyses of the fat and lipoid constituents of the blood serum, did not necessarily persist after formation of xanthomas.

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As mentioned at the beginning of this paper, *Charcot* and *Gombault* in 1876, succeeded in producing interstitial connective tissue growth by ligating the choledochal duct of animals. Following the ligation, on the third or fourth day, an enlargement of the perilobular spaces with beginning connective tissue proliferation occurred. These spaces appeared as islands, sometimes round, more often angular or triangular in form. Finally, the perilobular manifestations proceeded towards the center of the lobule destroying all liver cells in its path. Deep fissures resulted from this cell destruction which deranged the regular pattern of the remaining uninjured cells.

These experiments revealed that, also in man cirrhosis of the liver may result from disturbances of bile flow, thus the name biliary cirrhosis. Furthermore, two types have become recognized: the obstructive and the non-obstructive biliary cirrhosis.

The chief pre-disposing conditions of obstructive biliary cirrhosis are stone in the common duct, carcinoma at the head of the pancreas, adhesions around the common duct, congenital atresia of the bile ducts and parasitic infestation of the ducts. It is a rare disease. In 550 cases of liver cirrhosis of all types reporting by *Mallory*, obstructive biliary cirrhosis accouented for 24 or 4.4%.

The non-obstructive type of biliary cirrhosis was first described by *Hanot* in 1876 and in the literature is referred to as Hanot's cirrhosis or hypertrophic biliary cirrhosis. The description as written by *Hanot* himself, is: "Sclérose extralobulaire trés accusée et sans tendance à la rétraction du tissu conjonctif de nouvelle forma-

tion, souvent aussi sclérose intralobulaire; développement anormal et catarrhe chronique des canalicules biliares. C'est une affection qui s'accuse surtout par un ictère chronique dû à l'oblitération des canalicules biliares et par une hypertrophie considérable du foie, sans, l'ascite ni le développement anormal des veines sous-cutanées abdominales, qu'on observe dans la cirrhose classique. Le plus souvent cette affection a une marche lente et elle peut durer plusieurs années sans altérer profondément la nutrition; le plus souvent aussi, elle se termine par le syndrome designé sous le nom d'ictère grave."

Hanot summed up all these manifestations of his descriptions, in the name, "sclérose hypertrophique du foie avec ictère chronique".

In this early period, nothing was known about the liver function tests, the cholangiography or the biochemical knowledge that we have today, so that *Hanot* could not always differentiate between intrahepatic and extrahepatic obstruction and therefore, even though Hanot's description of the disease, might have been what we call today, primary biliary cirrhosis, we do not believe *Hanot* himself recognized it as a separate entity.

From the modern literature, is the case reported by *Klemperer* (1948), which he said, had clinical features and pathological findings quite similar to those originally described by *Hanot* and that *Hanot* had expressed the belief that the form of cirrhosis which he described originated in an inflammation of the bile radicals.

The pathologic change in the liver, chronic intrahepatic obliterating cholangitis was described in detail with a discussion of the pathogenesis by *Klemperer* (1948). He reported a patient who had chronic icterus for 3½ years together with frequent febrile attacks. Exploration and later autopsy revealed no evidence of obstruction of the main bile ducts. The liver function tests were pathological in the final stage of the illness and diffuse disease of the liver parenchyma seemed unlikely because of the long duration of the illness.

At autopsy, it was noted that intrahepatic medium sized and small bile canaliculi were surrounded and markedly narrowed by dense connective tissue. The lumen was frequently completely occluded by fibrous tissue. The liver cells were deeply icteric and showed severe degeneration with occasional focal necrosis. A conspicuously enlarged spleen showed the picture of chronic infectious splenic swelling on histologic examination. The diagnosis was biliary cirrhosis.

Today, it is well known that, aside from metabolic disorders, xanthomatous affections of the skin can accompany biliary cirrhosis. This is seen throughout the literature in the large number of cases reported under the name of xanthomatous biliary cirrhosis of the liver.

Although *Hanot* said that the chronic icterus and large size of the liver of his disease was due to obliteration of the intrahepatic bile ducts, it is noteworthy, that throughout his description, he never expressed the presence of skin changes of the patients who were affected with this disease, which are a frequent accompaniment of a long standing cholostasis.

Thannhauser and *Magendantz* in 1937 and *Thannhauser* in 1940, described "xanthomatous biliary cirrhosis" as a separate clinical entity. Today it is no longer considered as such but is recognized as a phase or period in the development of the full blown picture of primary cholostatic cirrhosis.

In 1949, *Ahrens* and *Kunkel*, described 18 cases of primary biliary cirrhosis and

the relationship between total serum lipids and the appearance of xanthelasma and xanthomas on the skin of these patients.

They maintained in their discussion, that all patients with a prolonged elevation of total serum lipids above 2000 mg.% developed severe generalized skin xanthomatas. Patients with total lipids below 1300 mg.% showed no xanthomata, while in the intermediate stage xanthelasma appeared.

W. E. Ricketts and *R. W. Wissler* (1949), presented a detailed report of nine cases of primary biliary cirrhosis. From their results of functional and electrophoretic studies, they maintained that this disease resembled manifestations of those found in obstruction of the biliary tract and not of the liver parenchyma.

H. Jesserer and *F. Wewalka* (1952), gave an account of a 61 year old woman with primary biliary cirrhosis and described skeletal modifications suggesting osteoporosis. The patient had very severe pain when she moved. However, being that she adhered very strictly to a fat poor diet, these changes were probably the result of faulty vitamine D metabolism. Following treatment with vitamine D for a period of three weeks, the clinical and roentgenological conditions returned to normal. It is noteworthy, that *Ahrens*, *Kunkel*, *Eisenmenger* and *Blondheim* (1949–1950), mentioned osteoporosis as one of the features which deserves special comment in their reports on the studies of 22 patients (17 of which had severe generalized skin xanthomatosis), in the six year period, 1944–1950.

The most recent and intensive studies with very comprehensive data, are the clinical, histological and pathological findings in six cases, by *L. Kallai* and *S. Cerlek* (title: The Clinic of Primary Biliary Cirrhosis), and in five cases by *H. A. Kuhn*, *W. Müller* and *R. Pfister*, published in May 1957.

Definition and differential Diagnosis

We wish to call this disease "primary cholostatic cirrhosis of the liver", because it is a cirrhosis which results from the long-standing bile stasis of the smaller bile ducts and canaliculi or cholangioles, and it is primary because the etiology of this cholostasis is not known as compared to secondary cholostatic cirrhosis, resulting from calculi in the intra- or extrahepatic bile ducts or other obstructions of the common bile duct.

The disease is characterized:

(1) Histologically: by a progressive development of fibrosis around the bile canaliculi with complete absence of any change of the extrahepatic bile ducts.

(2) Chemically: by signs of bile retention with only slowly developing disturbances of liver functions.

(3) Clinically: by icterus, chronic, varying in its intensity, but never leading to complete acholia.

(4) In some cases, by hypercholesterinemia accompanied at the same time by formations of xanthelasmas and xanthomatas.

(5) By affecting primarily the female sex in middle age.

(6) By a chronic course of many years and bad prognosis quoad vitam.

The significance of this rather rare disease lies primarily in its importance in differential diagnosis. It presents itself so completely with signs of a chronic obstruction icterus, that the differentiation from, the by far more frequent extrahepatic obstruction icterus from stone, stenosis or tumor, can be difficult, indeed, sometimes impossible. The chemical signs of bile retention-bilirubin, alkaline serum phosphatase, bromsulphalein excretion time are the same as by extrahepatic obstruction. The radiological discernment of the bile ducts is practically always impossible in the icteric stage because of the negative outcome. The liver function tests, which may be normal as well as completely or partly pathological, also give no differentiation. The laparoscopy pictures hardly differ significantly from those that are seen from an extrahepatic obstruction. The liver biopsy shows a relative characteristic appearance, that makes the diagnosis possible, however, only in the early stage; later, with increased development of connective tissue, the disease can no longer be differentiated from an ordinary portal cirrhosis.

From the above reasons, almost always, the differential diagnosis towards an extrahepatic obstruction, remains uncertain and therefore an exploratory laparotomy is undertaken. Indeed, this is today, in most cases, the only possibility, to confirm the diagnosis, in that it makes possible the proof of normal extrahepatic bile ducts. This happens most safely, without a doubt, with the help of intra-operative radiomanometry. At any rate, this is the rule with sufficient certainty in any case, only when the surgeon knows the disease; in various cases, the swollen lymphnodes, which are frequently present in the porta hepatis, have been wrongly taken as the cause of icterus and have been removed. To our knowledge in this disease, the laparoscopic cholangiography by *Royer*, has never been used, whereas, under certain circumstances, it may replace the exploratory laparotomy.

Synonyms for this disease are: primary biliary cirrhosis (*W. E. Ricketts* and *R. W. Wissler*, 1948); pericholangiolitic biliary cirrhosis (*H. E. MacMahon*, 1948); chronic obliterating cholangitis (*P. Klemperer*, 1948); non-obstructive cholangitic biliary cirrhosis (*S. S. Lichtman*, 1942); intrahepatic cholangitic biliary cirrhosis (*H. T. Karsner*, 1943); Hanot's biliary cirrhosis (*S. LaManna*, 1936).

The aims of the present investigation are, to present four observed cases, to collect all information from the literature and to describe the clinical picture of this disease.

Case reports

Case no. I, A. H. Age 36, F

Anamnesis

The patient's past history discloses that in her childhood she had pertussis and a middle-ear infection. In 1934 she underwent an appendectomy operation. In 1948 she was operated on for removal of a tubal pregnancy.

The present illness began in the summer of 1952 with weariness and nausea. These symptoms led the patient to visit her doctor and at that time a definite diagnosis was not made.

Beginning in January 1953, jaundice slowly made its appearance and two months later the patient had pruritus of the complete body surface. Since then she became more or less jauniced. Pains in the right upper abdominal quadrant, sometimes colic similar, occurred in the beginning of the jaundice phase in 1953. She never vomitted or had feeling to vomit: She never had swollen legs.

Since 1954 she has xanthelasmas and xanthomatas on different parts of her body; the eyelids and on the flexing surfaces of the elbow, fingers and foot. Because through conservative treatment no improvement occurred, on April 28, 1955, a laparotomy was performed in another hospital. At operation, no tumor, no metastasis, no stone or liver cirrhosis was found. Near the bile duct a few large lymph nodes were removed, which where considered to be the cause of obstruction. The post-operative course was without complications.

Seemingly, after the laparotomy, jaundice and pruritus diminished. However, because these symptoms never completely disappeared the patient was transferred to our hospital on October 17, 1955.

Status

This woman appeared in a well nourished condition. Her skin was dry, jaundiced and xanthelasmas and xanthomatas were present. The liver was enlarged and the spleen was not palpable. The patients complained of pain in the upper right abdominal quadrant.

Laboratory findings: 1955

Alkaline phosphatase	20.91 B-U
Bilirubin	6.1 mg.%
Total cholesterin	622 mg.%
Cholesterin esters	241 mg.%
Total protein	7.6 gm.%
Albumin	3.1 gm.%
Globulin	4.5 gm.%
Gamma globulin	17 units
RBC	3.85 mill.
WBC	4.250
Hb.	78%
Color index	1.1

Operation

The old laparotomy scar was excised and upon opening of the abdomen, a thick field of adhesions was encountered. The duodenum was solidly attached to the under surface of the liver, which was prominently enlarged. With a great deal of difficulty, the duodenum was finally liberated from the liver. The gallbladder was found to be very small and narrow. It was punctured and a dark green bile oozed out. A canula was inserted and a cholangiography was performed. Completely normal conditions of the biliary system were indicated. Then a liver biopsy was taken, a thin Pezzer catheter was used as a cholecystostomie, a Penrose drain was placed in the wound and the abdomen was closed.

Diagnosis: primary cholostatic cirrhosis of the liver.

Cholangiography

Following laparotomy, a cholangiography and manometry were performed. The cystic duct was overcome by a pressure of 16 cm. of water, the residual was 15 cm. X-rays were taken at pressures of 15, 20, 35, and 50 cm. of water. Completely normal conditions, of the intra- and extrahepatic biliary ducts were indicated. The papilla of Vateri was insignificant. The passage into the duodenum was not obstructed or hindered in any way. The intrahepatic ducts were rather thin, however, no sign of hindrance to bile flow was indicated.

Histology

An examination of the liver biopsy presented a liver cirrhosis with enlargement of glisson's capsule and an increased imigration of cells. There was building of bile thrombi without evidence of inflammation of the bile channels. In spots, icterus of the liver tissue was stronger, especially in those places where destruction of liver cells was seen. The histological diagnosis: liver cirrhosis with building of bile thrombi.

Catamnesis

The patient is alive today. She was last seen on July 1957. She appeared jaundiced, the liver was enlarged and xanthelasmas and xanthomatas of the skin were still present. She has no complaints aside from the jaundice and the xanthomatous changes of the skin. Her condition has remained more or less stationary.

The laboratory findings at this time (July 1957):

Alkaline phosphatase	15.72 B-U
Bilirubin	12.21 mg.%
Total cholesterin	270 mg.%
Total protein	8.11 gm.%
Albumin	3.38 gm.%
Globulin	4.73 gm.%
Gamma globulin	28 units
Thymol turbidity	20.5 units
Takata	+
Hanger	+
Weltman	0.15%
Sedimentation rate	118/136

Xanthelasmas (Case No. I). Xanthelasmas and xanthomas, appeared on this patient, one year after her first symptoms of jaundice and pruritus.

Epicrisis

This woman illustrates a typical case of primary cholostatic cirrhosis of the liver: the slow progression of the disease, the long-standing jaundice and pruritus, and enlarged liver and no indication of obstruction in the biliary system, as seen from a laparotomy and cholangiography.

Xanthelasmas and xanthomatas appeared one year after her first symptoms of jaundice and pruritus.

The laboratory findings point to all signs of a biliary obstruction (see under *Laboratory findings*).

Although after the histological findings no substantial inflammation of the bile channels was seen, it was decided, from the enlarged liver, the icterus with sign of progressing parenchyme destruction without essential histological changes of the liver cells, the high alkaline phosphatase value, xanthelasmas and xanthomatas, with certainty, upon a primary cholostatic cirrhosis of the liver.

Case no. II. R. B. Age 66, F

Anamnesis

It is important to note that in the family history of the patient a brother of 34 years died from tuberculosis of the lungs. Her husband, 66 years old, died from tuberculosis of the lungs and kidneys. Of the patient's three children a daughter has tuberculosis of the lungs.

The past history discloses that she had tuberculosis at the age of 35 years and was sent to a sanatorium for seven months. Later on, her uterine tubes were ligated because her husband had tuberculosis.

When the patient was 54 years old, she was in the clinic of internal medicine for treatment of bronchitis purulenta and intercurrent entero-colitis. In the same year

a throidectomy was done, the diagnosis was made the previous year. The liver was not palpable at that time.

The present disease relates back to 1945 when the patient was 55 years of age. She was hospitalized and treated for subacute rheumatic polyarthritis and for the first time an enlarged liver (4 cm.), was found. The Takata reaction was negative, the galactose test indicated a slightly delayed excretion time and the urine urobilinogen reaction was slightly positive.

In 1952 she had pleuritis, due perhaps to a reactivation of her old tuberculous lesion, and was sent, again, to a sanatorium for 8 months. Later, in the same year, a laparoscopy was performed and a small nodular hypertrophic cirrhosis and hepatosplenomegaly were found. The procedure was performed in another hospital. The continual sub-febrile temperature at that time, reacted promptly to antibiotic treatment. In December, the patient had chills, temperature of 39.2 and finally icterus and severe pruritus. She was transferred to the surgical clinic of another hospital. Here, on January 29, 1953, a laparotomy was performed. A cholecystostomy followed by cholangiogram, and a liver biopsy were made. The findings were: hepatosplenomegaly with small nodular hypertrophic liver cirrhosis; the cholangiogram indicated no obstruction in the biliary system.

She was transferred to the internal medicine clinic in 1954. Under treatment, the subfebrile temperatures disappeared and it was thought that the septical component causing the cholangiolitis, of the small intrahepatic biliary ducts, was destroyed.

However, in 1955, new symptoms appeared. The patient complained of cramp-like pains of the upper abdomen spreading to the back and girdle-like in the abdomen. The stools were a bright gray but the urine was not dark. She had subfebrile temperatures and said she felt tired. By use of a duodenal catheter and culture, staphylococcus aureus and streptococcus were found to be present.

On January 3, 1956, she was transferred to our surgical clinic. *Status:* The patient appeared as a small, very much undernourished, very old looking, overworked woman. Her skin was strongly creased, thin, brown, not icteric. She complained of severe girdle-like pains in the upper abdomen, especially in the right epigastric, respectively in the right hypochondrium.

On January 1956, a new cholecystostomy was made then followed by a cholangiogram. No hindrance to bile flow was indicated, completely normal conditions of the biliary system were found. She was transferred, with a cholecystostomy drain, to the internal medicine clinic on January 16, 1956, for further antibiotic treatment through the drain. A culture of the bile was made and pseudomonas aerigunosa, proteus morganii and enterococci were found to be present. Terramycin was injected intramuscularly and through the drain without any results, that is, an attempt to sterilize the bile could not be accomplished. The laboratory findings at this time were:

Serum protein	6.3 gm.%
	(albumin 3.1, globulin 3.2 gm.%)
Bilirubin	1.7 mg.%
Total cholesterin	171 mg.%
Thymol flocculation	+
Thymol turbidity	7.9 units
Sedimentation rate	78/115

Hepatosplenomegaly (Case no. II). Eleven years after the first signs of liver disease. The liver is enormously enlarged.

Her condition remained unchanged. After removal of the drain she was discharged from the hospital, further attempts to sterilize the bile seemed futile.

On May 5, 1956, the patient re-entered our surgical clinic. She admitted that since her discharge from the internal medicine clinic, she has had no abdominal pain but a large quantity of bile flows out of her fistula so that she must change the bandage at least once a day. For this reason she came to the surgical clinic, otherwise, she has no complaints.

Status: Upon examination, the patient was found in an undernourished condition. She had no icterus but the skin was pigmented a diffuse brown. The liver was palpable 5 cm. below the costal arch and the margin was not sharp.

She was operated on May 1956 (see *Operation report*). The post-operative course was without complications. Jaundice remained unchanged.

Laboratory findings: 1956

Total protein	7.74 gm.%
Takata	+
Thymol turbidity	8.9 units

Gamma globulin	10 units
Alkaline phosphatase	19.33 B-U
Serum bilirubin	3.88
RBC	3.65 mill.
WBC	3,400
Hb.	73%
Color index	1.0

Operation

The old scar with fistula area was excised and the incision extended until the fundus of the gallbladder appeared. After the abdominal wall and the gallbladder were isolated, the widespread adhesions were removed until the stomach, duodenum, choledochus and cysticus became prominently exposed. The choledochus was extremely narrow, the hapatic artery was extraordinarily thick and tortuous. On the stomach and duodenum, one found neither ulcus, nor scar of one having existed, nor evidence of a diverticula of the duodenum. The gallbladder was narrow and contained no concrement. The cysticus was ligated and a canula placed and tied in the choledochus and a cholangiography followed. Then the cysticus was out, the gallbladder was disconnected and removed, and the liver bed was sutured with chromic catgut. A large lymphgland was removed from around the neck of gallbladder. Then a liver biopsy was taken and after the placing of a Penrose drain the abdomen was closed.

Diagnosis: primary cholostatic cirrhosis of the liver.

Cholangiography

Normal conditions persisted throughout the extra- and intrahepatic ducts, no indication of obstruction. The passage pressure was 13 cm. of water and the residual pressure was 11 cm. The extra- and intrahepatic ducts were rather narrow. X-rays were taken at pressures of 13, 10 and 40 cm. of water.

Histology

Histologically, the gallbladder showed a severe connective tissue proliferation especially in the subserosa; the mucous membrane being slightly affected.

The liver biopsy showed an extensive "Umbau" of the liver tissue with irregular pseudo-lobules and often small areas of regeneration. Outstanding was the rather severe round cell infiltration of the broadened portal fields. Bile duct proliferation was seldom seen, the existing bile ducts seemed dilated. The liver cells showed irregular fatty degeneration; often with storage of bile pigment, no hemosiderin. All in all, one received the impression of an uncharacteristic portal cirrhosis without evidence of a primary cholostatic process.

The lymph gland removed from the neck of the gallbladder had a decreased consistency and hyperemia.

Diagnosis: (1) Chronic cholesystitis
(2) Portal liver cirrhosis (Laennec type)
(3) Decreased consistency and hyperemia of lymphnode.

Catamnesis

The patient entered our surgical clinic on January 3, 1956. Her skin was brown, not icteric. She complained of severe girdle-like pains in the upper abdomen.

An exploratory laparotomy followed by a cholangiography showed completely normal conditions of the biliary system. No signs of obstruction to bile flow were indicated (see *Cholangiography*).

Her condition remained unchanged, until May 1956, when she re-entered our clinic for treatment of her bile fistula. She had no abdominal pain. Her skin was icteric and pigmented by a diffuse brown. The liver was palpable 5 cm. beneath the costal arch.

Following cholecystectomy (see *Operation*), she was discharged from the hospital. She has not been seen ever since.

Epicrisis

The disease of this woman relates back to 1945 when she was 55 years of age. The liver, at that time, was found to be enlarged 4 cm. beneath the costal margin and the galactose indicated a slightly delayed excretion time.

In 1952, she had a laparoscopy in another hospital, where a small nodular hypertrophic cirrhosis and enlarged spleen were found.

In 1956 she entered our surgical clinic and an exploratory laparotomy followed by cholangiography and liver biopsy was performed (see *Operation*, etc.).

Her condition had remained the same during her stay in our hospital. She was discharged in 1956 and has not been seen since that time.

Case no. III. B. U. G. Age 53, F

Anamnesis

The past history of the patient was insignificant. The present illness began in 1952, when she had a stubborn pruritus, and in November of the same year jaundice appeared.

On May 1953, she was hospitalized in the internal medicine clinic where her condition was diagnosed as primary pericholangiolitic liver cirrhosis. They supported this diagnosis from: the presence of a large hard liver (4 cm. beneath the costal arch), the reduced liver-function tests, high alkaline phosphatase values, normal filling and emptying of the gallbladder, and a normal Bromsulfalein test. The laparotomy findings: the liver was very much enlarged and appeared dark red and not green as is usually seen with biliary cirrhosis. Also, by means of laparoscopy a yellow deposition was observed on the liver surface that could not be interpreted.

At this time intensive antibiotic therapy was carried out and continued for a time after her discharge from the hospital. No improvement resulted from this treatment. The pruritus became so severe that only through repeated duodenal drainage, did she receive relief. Now, the bilirubin concentration increased from 2 to 7 mg.%. She was advised and agreed to undergo an exploratory laparotomy and temporary drainage.

The patient entered our surgical clinic on May 1954. An exploratory laparotomy, cholangiography, followed by a liver biopsy were performed on May 14, 1954 (see under *Operation*, *Cholangiography* and *Histology*). A sample of bile removed during operation, was found sterile. Post-operatively no complications arised.

On June 3, 1954, another cholangiography was done and like the previous one, indicated no signs of obstruction to the flow of bile. The patient said she felt well, her appetite was good and icterus has decreased. The bilirubin value was 10.34 mg.% her pruritus was sleight. The liver was palpable 4 cm. below the costal margin. She was discharged from the hospital on June 16, 1954.

Laboratory findings: 1954

Alkaline phosphatase	6.8 B-U
Bilirubin	7.4 mg.%
Serum Protein	8.4 gm.%
Sedimentation rate	42/80

Operation

On May 14, 1954, an exploratory laparotomy and cholangiography followed by a liver biopsy, were performed.

An incision below the right costal arch was made. Upon opening of the abdomen the gallbladder immediately presented itself, and was found without adhesions or concrement. The fundus was punctured and followed by a cholangiography which indicated completely normal conditions of the biliary system. A T-drain was inserted and sutured in the common duct. A liver biopsy fowed and the incision was closed.

The diagnosis: primary biliary cirrhosis of the liver.

Cholangiography

After puncture of the fundus of the gallbladder a normal pressure of 21 cm. of water was found. Normal passage of the cystic duct was indicated and the common duct, which was rather narrow, corresponded to 12 cm. water pressure. A cholangiogram showed completely normal conditions. The papilla indicated no hindrance to bile flow and the intrahepatic ducts were of normal size and distribution with no signs of obstruction.

Histology

Histologically, the liver biopsy showed a cirrhosis with intensive bile stasis. The amount of connective tissue was increased and round cell infiltration was present. Granulocyte infiltration was also present. There was very little disposition of lipid in the liver tissue. The cholostasis is very distinct and bile cylinders are present. The diagnosis was biliary cirrhosis.

Catamnesis

This patient entered our surgical clinic in 1954. She was icteric, her liver was enlarged 4 cm. below the costal margin. She said her appetite was good and, except for icterus and periodic pruritus, she felt well. She was discharged from our hospital on June 16, 1954.

She became progressively worse with all the signs of liver insufficiency and died on May 10, 1955 (see *Autopsy report*).

Epicrisis

The patient's disease began, in 1952, with a stubborn pruritus and a gradual appearence of jaundice.

She was treated with antibiotics resulting in no improvement of her condition in the internal medicine clinic, in 1954.

In the same year she entered our surgical clinic and underwent an exploratory laparotomy followed by cholangiography and liver biopsy. No obstruction or hindrance to bile flow was found during operation and the cholangiograms indicated complete normal conditions of the bile ducts. She was discharged in 1954.

Her condition became progressively worse with development of ascites, esophageal varices and coma and she died on May 10, 1955 (see *Autopsy report*).

Autopsy report: May 10, 1955

The consistency of the liver was slightly increased and a finely granulated liver cirrhosis with shrinkage of the right lobe was prominent.

Many adhesions between organs and surrounding tissue were found: scattered areas of the capsule of the liver were attached to the diaphragm while the under surface was attached to the duodenum; the stomach was also attached to the diaphragm.

Ascites was present and 700 cc. of fluid were removed. The spleen was enlarged and the consistency increased.

Severe icterus of the external as well as the internal body surfaces was seen: icterus of the intimal walls of the blood vessels and sklerae, severe icterus of the skin with brown pigmentation (melanosis), severe icterie nephrosis, brown degeneration and icterus of the myocard.

The papilla duodeni presented itself rather prominently. The right heart was dilated and a wide-open foramen ovale was found. Sclerosis of the mitral valve was present.

No fat was present in the adrenal cortex. There was bleeding of the mucous membrane of the larynx. Partly devastated goiter nodules of the thyroid were seen. The uterus was slightly hypoplastic. There was bleeding of the mucous membrane of the urinary bladder.

The stomach had a severe mucous hypertrophic gastritis. A small chronic duodenal ulcer with fine mucosa scars of the superior section with edema of the duodenal mucosa was found. On the pancreas, were seen multiple fine fatty tissue necrosis. Separate openings for the common duct and for the pancreatic duct were present.

The tonsils were scarred. Varicosities on the lower extremities were present. There was slight swelling of the brain with hyperemia of the meninges and osteoporosis of the skull.

Case no. IV, E. H. T. Age 66, F

Anamnesis

The family history of this patient, discloses that her mother died from stomach carcinoma and the father from a heart attack. Her past history, reveals that she had diphtheria and in 1927 pneumonia of both lungs, which, under treatment, seemingly, completely healed.

In 1954, the patient was under treatment for a stomach ulcer and diabetes mellitus. She took insulin for one year, then discontinued and never kept a strict diet.

In 1955, she developed a furuncle on the buttocks and big toe with much pus formation. She has had a progressing necrosis of the right heel for the past 6 months.

On April 26, 1956, she entered the internal medicine clinic for treatment of diabetes mellitus, gangrene of the right heel, cystitis, and icterus. The laboratory

findings were: Alkaline phosphatase (37 B-U), Bilirubin (2.8 mg.%), Takata +, Hanger +, Thymol 9.5 units. A duodenal catheter showed the presence of bile when oil was used as the means of stimulating excretion. Bromsulfalein appeared 33 minutes after intravenous injection. The high alkaline phosphatase and pathological flocculation tests of the liver, indicated bile stasis with biliary cirrhosis, the patient was thought to have an obstruction icterus and was transferred to our surgical clinic.

Status: On June 15, 1956, she appeared in our surgical clinic jaundiced, with dry skin and in a poorly nourished condition. The liver was 10 cm. beneath the costal margin, the spleen was not palpable. She also had a nodular goiter and a suppurating necrotic gangrene of the medial side of the right heel.

She was operated on June 21, 1956. A cholecystostomy, cholangiography, amputation of the necrotic heel followed the exploratory laparotomy (see *Operation*).

On August 10, 1956, the right leg was amputated above the knee to prevent further spread of gangrene. The wound healed without complications. The condition of the patient has remained stationary for the past four weeks. She was discharged from the hospital on November 22, 1956, and has been in the old-age asylum ever since.

Laboratory findings: 1956

Alkaline phosphatase	38 B-U
Bilirubin	2.8 mg.%
Total cholesterin	280 mg.%
Thymol flocculation	++
Takata	+
Albumin	31.2% (normal 57.3%)
RBC	3.73 mill.
WBC	6600
Hb.	70%
Color index	0.93
Sedimentation rate	130/140
Globulin	68.8% (normal 42.7%)

Operation

Upon opening of the abdomen, the liver was enlarged a hand's breadth below the costal margin. The consistency was increased and a very fine granulating surface was seen. The gallbladder was small, free of concrement, flaccid; the common duct was narrow and surrounded by large lymph nodes; the pancreas was normal. A tobacco pouch suture was made in the gallbladder and a cholangiography was performed, followed by a large biopsy of the liver. The canula in the fundus of the gallbladder was removed and replaced by a Pezzer catheter which led out of the abdomen (cholecystostomy). A Penrose was inserted in the abdomen and the wound was closed.

Diagnosis: primary cholostatic liver cirrhosis.

Cholangiography: 1956

A tobacco-pouch suture was made in the gallbladder, a canula was inserted and a cholangiography was made. A passage pressure of 14 cm. and a residual pressure

of 11 cm. of water were found. Cholangiograms were made with 14, 16, 25, an 45 cm. water pressures. They indicated a completely unsuspicious, normal intra- and extrahepatic biliary system, with no presence of concrement, stenoses or dilations.

Histology

Histologically, we see a certain "Umbau" of the liver parenchyme that does not confer to a cirrhosis but more to a fibrotic process. The areas of Glisson (continuation of capsule), are somewhat enlarged and show cleavage near the periphery of the lobules.

The portal fields are strongly infiltrated with lymphocytes, histiocytes and some granulocytes. Here and there the bile ducts indicate an inflammatory process or are completely free of pathological signs. One cannot speak of cholangitis from this evidence.

The peripheral epithelium in the periphery of the lobules indicates an icteric color; also we find bile thrombi in this area quite often.

The liver cells themselves show definite regressive changes, mainly the Kupffer cells are strongly adipose, this is significantly seen by use of the Sudan stain.

The pathological picture presents all the signs of a cholostatic process with reactive fibrosis, not a genuine cirrhosis.

The pathological diagnosis reads

We see areas showing the presence of icterus with bile thrombi in the bile capillaries; a slight enlargement of the portal areas with round cell infiltration. Fatty deposition in the Kupffer cells with no cirrhosis present in the examined region.

Catamnesis

This woman is still living and was seen again on August 13, 1957. Her condition is poor. She is markedly jaundiced and has generalized pruritus; the liver is enlarged 10 cm. beneath the costal margin and is very painful upon pressure; the spleen is not palpable, xanthelasma of the lower lid of the right eye and melanosis of the skin are seen. The patient says her abdomen has increased in circumference, however, ascites was not prominent. The patient's appetite is poor and she has frequent periods of vomiting and diarrhea. Aside from the development of bed sore no new complications have occurred.

Epicrisis

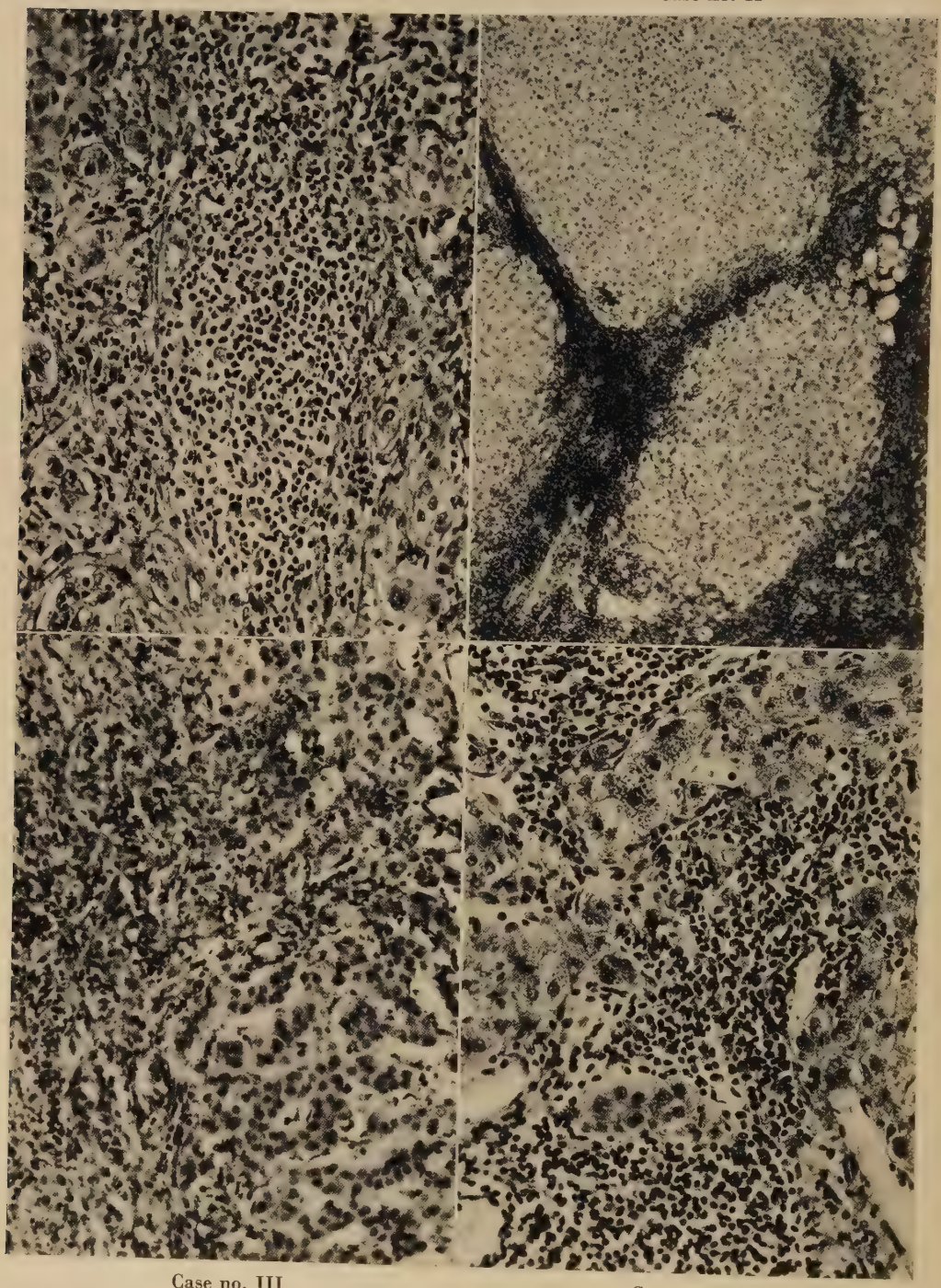
The patient was operated in our surgical clinic because it was thought that she had obstruction icterus. At operation a primary biliary cirrhosis was diagnosed, therefore, only a cholecystostomy with cholangiography and liver biopsy was performed. The wound after removal of the cholecystostomy drain,, healed without complications.

This woman also had a progressing gangrene of the right heel which led to amputation of the right leg above the knee. The stump healed well.

The condition of the patient today is poor. Striking symptoms are jaundice, pruritus and enlarged liver with signs of ascites.

Case no. I

Case no. II



Case no. III

Case no. IV

Survey of the Literature

I. Introduction:

We present 69 cases from the literature which we believe are the best representatives of primary cholostatic cirrhosis of the liver. Unfortunately, it was not possible to gather all cases reported because the papers were not available. All the important findings, clinical and chemical, when given, have been included in the following tables. Only cases with proven diagnosis and sufficient clinical details are reported in this paper.

II. Tables: *The symbols and their meanings as used in the tables*

J Jaundice
P Pruritus
Pa. Pain
D Diarrhea
Po. Poor
Go. Good
no. normal
B-U Bodansky units
K-U King-Armstrong units
RBC Millions/mm^3
WBC Thousands/mm^3

The enlargement of the liver and spleen is given in cm. below the costal margin.

Serum iron and copper are given in gamma percent.

All flocculation tests are given in strength of their pathogenicity (+, ++, etc.).

Liver biopsy (Case no. I). Liver cirrhosis with enlargement of the periportal fields, increased cell infiltration and bile thrombi without evidence of inflammation of the bile channels. Icteric liver tissue, especially in those places, where destruction of liver cells is seen. 230×

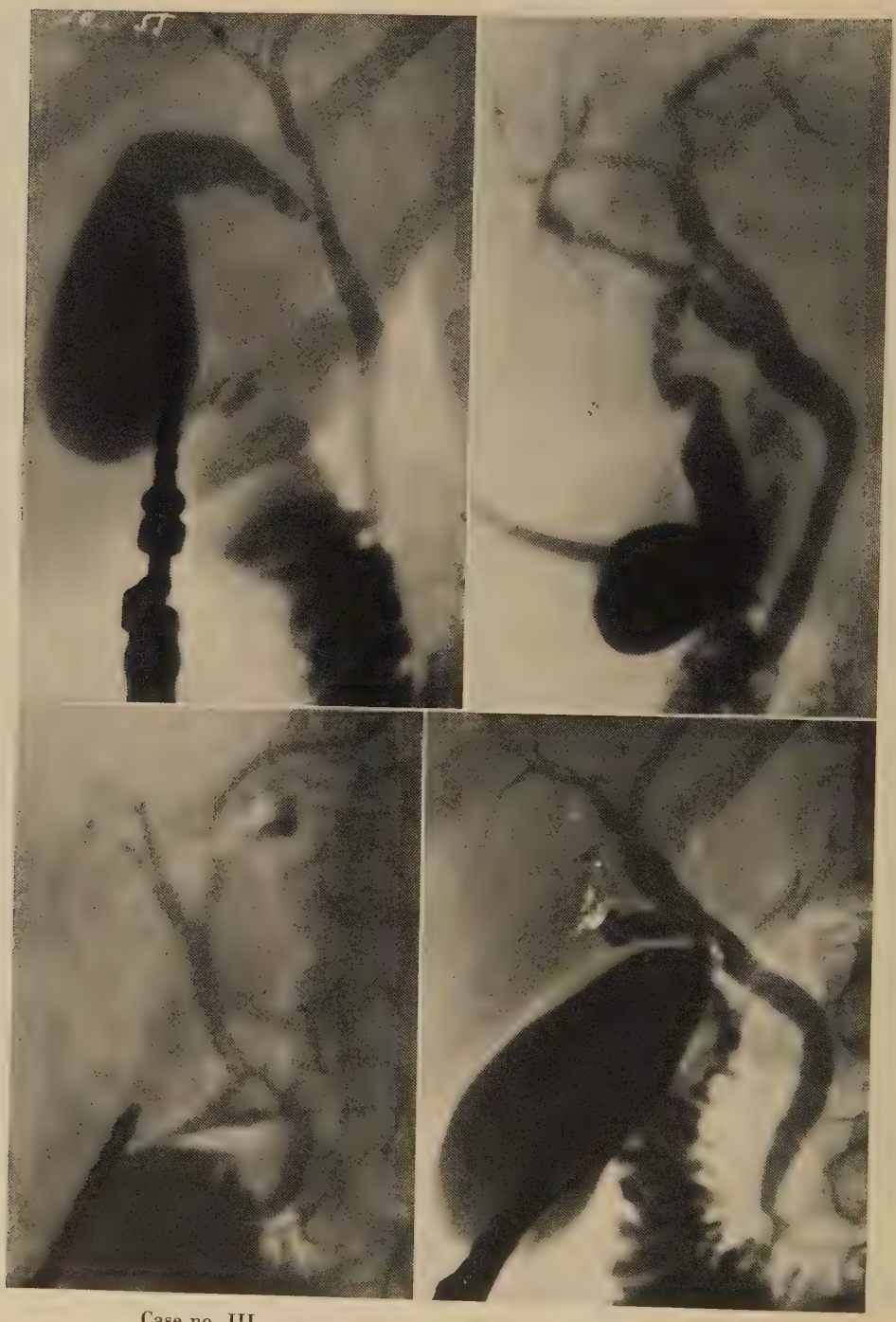
Liver biopsy (Case no. II). Irregular pseudo-lobules and often small areas of regeneration with rather severe round-cell infiltration of the broadened portal fields. Irregular fatty degeneration of the liver cells. 70×

Liver biopsy (Case no. III). Liver cirrhosis with intensive bile stasis. Round-cell infiltration and an increase of connective tissue. 180×

Liver biopsy (Case no. IV). The portal fields are strongly infiltrated with lymphocytes, histiocytes and some granulocytes. The liver cells are icteric and show definite regressive changes. 230×

Case no. I

Case no. II



Case no. III

Case no. IV

\+ Symptom present, test pathological or a procedure has been carried out (laparotomy, etc.).

— Symptom absent, test not pathological or procedure not performed.

(+) Test pathological but not significantly.

Weight loss is given in kilograms.

The sedimentation rate is given sometimes for the first and second hour and sometimes for the first only.

1:16 Test positive with this dilution.

The numbers of the cases taken from the literature are written after the corresponding authors under, *references used in the survey of cases from the literature*, of the bibliography.

Discussion

We wish to present, in our survey of 73 cases, 69 from the literature and four from our hospital (Surgical Clinic, Basle University), the outstanding behaviour patterns of this disease. A review of our tables shows:

Age:

We find that the age in this servey of cases, ranges from 10 to 68 years, the concentration being within the 41 to 59 years limit. Twenty-four cases belong to this group (Case no. 6, 8, 10, 11, 13, 22, 27, 49 to 55, 58, 60, 64, 66–69, III). Eight patients are in their late thirties (Case no. 4, 16, 17, 21, 47, 56, 59, 65, I), and six in their early sixties

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Cholangiography (Case no. I). The cystic duct was overcome by a pressure of 16 cm. of water. The residual pressure was 16 cm. of water. Completely normal conditions of the biliary system are seen, no hindrance to bile flow is present.

Cholangiography (Case no. II). The passage pressure was 13 cm. of water, the residual pressure was 11 cm. Normal conditions persist throughout the intra- and extrahepatic biliary systems; no obstruction or hindrance to bile flow is indicated.

Cholangiography (Case no. III). After puncture of the fundus of the gallbladder, a normal pressure of 21 cm. of water was found. The cystic duct was overcome by a pressure of 12 cm. of water. No signs of obstruction to bile flow are seen in the extra- and intrahepatic biliary systems.

Cholangiography (Case no. IV). A passage pressure of 14 cm. and a residual of 11 cm. of water were found. No sign of obstruction in the extra- or intrahepatic ducts is indicated.

	Case no.	1	2	3	4	5	6	7	8	9	10	11	12
Particulars from the anamnese	Age	60	29	29	37	27	44	19	44	64	47	45	61
	Sex	F	M	M	F	M	F	F	F	F	F	F	M
	Duration of disease	12	2	4	3	3	4	4	6	7	4	17	3
	First symptom	P	J	J	P	P	P	Pa.	P	P	P	P u. J	P
	Appetite		G	G	G	G	G	Po.					
	Wt. loss	+	6	2.5	4	10	8	3					
Clinical symptoms	Pruritus	+	+	+	+	+	+	+	+	+	+	+	+
	Jaundice	+	+	+	+	+	+	+	+	+	+	+	+
	Abdominal pain	—	+	+	+	+	—	+					
	Chills	—	—	—	+	—	—	+					
	Temperature	—	—	—	—	+	—	+			+		
	Diarrhea												
Physical examination													
Skin	Melanosis	—	+	+	+	+	+	+					
	Pyoderma	—	—	+	+	+	+	+					
	Xanthelasma	+	—	+	+	+	+	—				+	
	Xanthoma	—	—	—	—	+	+	—				+	
	Spiders	—	—	—	—	—	+	—					
	Erythema palmaris	—	—	+	+	—	—	—					
Abdomen	Enlarged liver	10	4	10	10	3	8	2			7		
	Enlarged spleen	+	6	4	2	2	2	3					
	Ascites												
Blood picture	Erythrocytes		4.1	4.9	4.0	4.4	3.8	4.1	3.4	4.1	3.15		
	Leucocytes		4.4	11.6	6.8	7.0	6.0	11.6	4.9	7.0	10.0		
	Hemoglobin								9.2	13.3	11.2		
	Color index								0.83	1.0	1.1		
	Sedimentation rate	57/91	10/36	110/130	60/86	45/80	80/120	95/122	124/140	54/92	141/145	27/62	48/80

Laboratory findings													
Liver function	Thymol turbidity	+	10	20	20	8	20	17	+	+	+	+	+
	Thymol flocculation	+	+2	+5	+4	+2	+5	+5					
	Gold flocculation		+2	+4	+3	+1	+5	+5					
	Cephalin flocculation												
	Bromsulfalein												
	Takata	+											
	Galactose								no.	no.	no.	no.	no.
Blood chemistry	Total lipid												
	Total cholesterine	460	152	864	550	577	670	198	695	300	500	205	375
	Cholesterine esters								577	219	325		
	Phospholipids		228	875	1480	1175	1880	423	1380				
	Serum bilirubin	17	5.35	29.4	4.06	8.77	5.35	10.16	0.87	2.66	19.69	23.8	3.69
	Serum iron		178	124	258	224	263	81	185	140	109	70	96
	Serum copper								271	163	197	228	234
	Alkaline phosphatase	48 K-A	23 B-U	47.86	25.97	48.13	43.75	18.12	27.8	9.5	19.7	11.2	12.7
	Total protein	6.4	7.34	8.62	8.43	7.25	9.37	9.0	9.6	8.6	8.2	5.8	8.6
	Albumin		3.66	3.35	3.68	3.78	4.06	3.87	4.0	3.9	2.6	2.5	3.4
	Globulin		3.68	5.27	4.75	3.47	5.31	5.15	5.6	4.7	5.6	3.3	5.2
	Prothrombin		89.2	75	81.3	89.2	81		110	100	50	48	94
	Weltman test								7	8	4	8	7
Urine and stool	Urine bilirubin	+	+	+	(+)	+	(+)	+					
	Urobilinogen	1:16	+	+	+	+	+	+					
	Stercobilin		—	—	–	—	—						
	Fat in stool	+	+	—	—	+	+	—					
Surgery performed	Laparotomy	+	+	—	+	+	+	+	+	+	+	+	+
	Laparoscopy								+	+	+	+	—
	Cholangiography		+	+	+	+	+	+					
	Liver biopsy	+	+	+	+	+	+	+	+	+	+	+	+

	Case no.	13	14	15	16	17	18	19	20	21	22	23	24
Particulars from the anamnese	Age	51	47	48	36	36	42	27	27	36	51	10	63
	Sex	F	M	F	F	F	M	M	F	F	F	M	F
	Duration of disease	1	4	34	10	3	6	7	7	1	2	8	1
	First symptom	J u. P	P u. J	Pa.		J		P	P	J	J	D	J
	Appetite	Po.	Po.				Po.						
	Wt. loss	10				5	15					15	22
Clinical symptoms	Pruritus	+	+	+	+	+	+	+	¬	+	—		+
	Jaundice	+	¬	+	+	+	+	¬	+	+	+		+
	Abdominal pain			+	—	—	—	—	—	—	—	+	
	Chills			+	+	—	—	—	—	—	—		
	Temperature			+	+	+	—	—	—	—	—	+	
	Diarrhea			+								+	
Physical examination													
Skin	Melanosis												
	Pyoderma											—	—
	Xanthelasma				+	+	+	+	+	+		+	—
	Xanthoma				+	+	+	+	+	—	—	—	—
	Spiders						+				—	—	—
	Erythema palmaris											—	—
Abdomen	Enlarged liver	2	+	15	6	7	7	5	5	6	7	6	8
	Enlarged spleen		+	4	+		7		+	+	+	+	—
	Ascites				+		+				¬		
Blood picture	Erythrocytes	4.0			2.61	4.4	3.7	4.7	4.4	3.8	4.0	4.2	3.73
	Leucocytes	6,1	6,9		5,85	9,0	6,0	7,1	17,6	12,8	5,2	17,6	9,4
	Hemoglobin	9.45	14.4		80	66	70	85	13.2	10.7	12.6	10.2	13.5
	Color index	0.79			1.5	0.75	0.94	1.4	0 93	1.05	0.97	0.76	1.16
	Sedimentation rate	64			42								

Laboratory findings													
Liver function	Thymol turbidity				15.7		20	14.4	21				
	Thymol flocculation				3+		3+						
	Gold flocculation												
	Cephalin flocculation	3+							4+	4+	4+	1+	4+
	Bromsulfalein		19%					40%					
	Takata				2+								
	Galactose												
Blood chemistry	Total lipid						2095	5040	6745	2200			
	Total cholesterine	390	520	300	1172	2200	616	1490	2050	580	270		850
	Cholesterine esters				332		129.4	127	995	150	115		
	Phospholipids				80		787.5	2925	1395				
	Serum bilirubin	4.5	2.0	2.5	5.4	4.5	16.5	4.3	3.6	8.8	2.5	4.3	8.8
	Serum iron												
	Serum copper												
	Alkaline phosphatase	22	25	10	77.3		8.7	46	34	40.5	40	16.9	121
	Total protein				7.0	9.1	8.7	7.79	8.9	7.6	7.02	6.75	7.56
	Albumin	3.5	4.5	3.7	3.65	4.0	2.7	2.15	4.15	4.1	3.47	3.38	
	Globulin	3.2	2.7	3.8	3.36	5.1	6.0	5.14	4.75	3.5	3.55	3.37	
	Prothrombin	100	100				100		90	100	90	100	97
	Weltman test												
Urine and stool	Urine bilirubin	6	13	14	+		+	+					
	Urobilinogen				+					+	+	0.13	
	Stercobilin												
	Fat in stool					+	+	+					
Surgery performed	Laparotomy	+	+	+					+			+	+
	Laparoscopy	+											
	Cholangiography	+										+	+
	Liver biopsy	+	+	+	+				+				

	Case no.	25	26	27	28	29	30	31	32	33	34	35	36
Particulars from the anamnese	Age	64	22	41	16								
	Sex	M	F	F	M	F	F	F	F	F	F	F	F
	Duration of disease	1	12	3	14								
	First symptom	D	J u. P	P	D								
	Appetite												
	Wt. loss	22		40	7								
Clinical symptoms	Pruritus	+	+	+	+	+	+	+	+	+	+	+	+
	Jaundice	+	+	+	+	+	+	+	+	+	+	+	+
	Abdominal pain												
	Chills												
	Temperature												
	Diarrhea	+			+								
Physical examination													
Skin	Melanosis	—	—	—	—	—	—	—					
	Pyoderma	—	—	—	—	—	—	—					
	Xanthelasma	—	—	—	—	—	—	—					
	Xanthoma	—	—	—	—	—	—	—					
	Spiders	—	—	—	—	—	—	—					
	Erythema palmaris	—	—	—	—	—	—	—					
Abdomen	Enlarged liver	10	7	+	3	+	+	+	+	+	+	+	+
	Enlarged spleen	+	+	+	+								
	Ascites												
Blood picture	Erythrocytes	3.22	3.16		4.1								
	Leucocytes	6,55	13,5		4,4								
	Hemoglobin	10.5	11.5		11.5								
	Color index	1.0	1.1		0.87								
	Sedimentation rate												

Laboratory findings													
Liver function	Thymol turbidity	5.5											
	Thymol flocculation												
	Gold flocculation												
	Cephalin flocculation												
	Bromsulfalein												
	Takata												
	Galactose												
Blood chemistry	Total lipid					758	1000	1193	1230	1269	1355	1385	1615
	Total cholesterine	355	160			208	325	463	432	425	387	442	583
	Cholesterine esters	103	53										
	Phospholipids					328	386	406	363	494	425	587	844
	Serum bilirubin	22.64	11.20										
	Serum iron												
	Serum copper												
	Alkaline phosphatase	23											
	Total protein	6.96	7.21										
	Albumin	3.6	2.29										
	Globulin	3.4	4.91										
	Prothrombin	77											
	Weltman test												
Urine and stool	Urine bilirubin												
	Urobilinogen	0.2	0.05										
	Stercobilin												
	Fat in stool												
Surgery performed	Laparotomy	+	+	—	+								
	Laparoscopy												
	Cholangiography												
	Liver biopsy	+	+	—	+								

	Case no.	37	38	39	40	41	42	43	44	45	46	47	48
Particulars from the anamnese	Age	F	F	F	F	F	F					39	29
	Sex							F	F	F	F	F	F
	Duration of disease											11	7
	First symptom												
	Appetite												
	Wt. loss												
Clinical symptoms	Pruritus	+	+	+	+	+	+	+	+	+	+	+	+
	Jaundice	+	+	+	+	+	+	+	+	+	+	+	+
	Abdominal pain												
	Chills												
	Temperature												
	Diarrhea												
Physical examination													
Skin	Melanosis						—	—	—	—	—	—	+
	Pyoderma												
	Xanthelasma						—	+	+	+	+	+	+
	Xanthoma						—	+	+	+	+	+	+
	Spiders						—	—	—	—	—	—	—
	Erythema palmaris						—	—	—	—	—	—	—
Abdomen	Enlarged liver	+	+	+	+	+	+	+	+	+	+	12	12
	Enlarged spleen						—	—	—	—	—	+	+
	Ascites												
Blood picture	Erythrocytes											4.82	4.18
	Leucocytes											9,0	15,0
	Hemoglobin											16.5	15.2
	Color index											1.04	1.1
	Sedimentation rate											47	50

Laboratory findings													
Liver function	Thymol turbidity											33	22
	Thymol flocculation												
	Gold flocculation												
	Cephalin flocculation												
	Bromsulfalein											24	24
	Takata												
	Galactose												
Blood chemistry	Total lipid	1641	1678	1754	1927	1933	1943	2173	2346	2693	3017	3068	2500
	Total cholesterine	416	608	571	675	800	566	691	650	866	1070	1046	833
	Cholesterine esters												
	Phospholipids	706	608	571	675	939	995	1110	1350	1525	1688	1688	1395
	Serum bilirubin											14.6	9.8
	Serum iron												
	Serum copper												
	Alkaline phosphatase											116	52
	Total protein											7.7	7.3
	Albumin											3.7	4.3
	Globulin											4.0	3.0
	Prothrombin											100	100
	Weltman test												
Urine and stool	Urine bilirubin												
	Urobilinogen											+	+
	Stercobilin												
	Fat in stool												
Surgery performed	Laparotomy											+	+
	Laparoscopy												
	Cholangiography												
	Liver biopsy											+	+

	Case no.	49	50	51	52	53	54	55	56	57	58	59	60
Particulars from the anamnese	Age	43	42	44	42	51	49	49	35	34	44	35	59
	Sex	F	F	F	F	F	F	F	F	F	F	F	F
	Duration of disease	5	5	3	3	2	2	7	6	5	4	3	2
	First symptom												
	Appetite												
	Wt. loss												
Clinical symptoms	Pruritus	+	+	+	+	+	+	+	+	+	+	+	+
	Jaundice	+	+	+	+	+	+	+	+	+	+	+	+
	Abdominal pain												
	Chills												
	Temperature												
	Diarrhea												
Physical examination													
Skin	Melanosis	+	+	—	+	—	—	—	+	+	+	+	+
	Pyoderma				—	—	—	—	—	—	—	—	—
	Xanthelasma	+	+	+	+	+	+	+	+	+	+	+	+
	Xanthoma	+	+	+	+	+	+	—	—	—	—	—	—
	Spiders	+	+	—	—	+	+	—	+	—	—	—	—
	Erythema palmaris	—	+	+	+	—	—	—	+	—	—	—	—
Abdomen	Enlarged liver	9	9	14	13	13	8	17	14	10	10	10	10
	Enlarged spleen	+	+	—	+	—	—	—	+	—	—	+	+
	Ascites												
Blood picture	Erythrocytes	4.4	3.95	4.2	4.2	3.87	4.8	4.0	3.7	3.8	4.0	4.9	4.0
	Leucocytes	33,0	5,8	11,5	9,5	12	12	8,0	7,5	13	12	6,1	5,9
	Hemoglobin	13.5	13.2	14.3	13	13	14	13	13	13	13.5	13	12
	Color index	0.97	1.03	1.05	0.96	1.0	0.93	1.0	1.0	1.0	1.0	0.87	0.93
	Sedimentation rate	64	57	59	83	54	7P	53	45	53	27	50	52

Laboratory findings													
Liver function	Thymol turbidity	25		24	44	44	27	17	7	8	8	25	3
	Thymol flocculation												
	Gold flocculation												
	Cephalin flocculation												
	Bromsulfalein	32	29	29	24	22	35	24	28	24	26	27	22
	Takata												
	Galactose												
Blood chemistry	Total lipid	2240	1390	3143	3250	2316	1812	1743	1019	1422	1478	1561	1002
	Total cholesterine	800	375	1066	620	878	490	516	279	483	502	479	317
	Cholesterine esters												
	Phospholipids	960	656	1650	1688	1200	1196	688	406	531	531	687	394
	Serum bilirubin	34.8	15	11.9	26	11.9	14	22	3.4	3.1	3.6	16	1.0
	Serum iron												
	Serum copper												
	Alkaline phosphatase	106		80	40	94	67	76	44	70	62	88	15
	Total protein	8.0	8.2	7.5	9.4	6.6	6.8	7.3	7.8	7.7	6.4	8.3	7.8
	Albumin	4.5	5.8	3.5	4.5	3.6	4.5	3.3	3.9	4.2	3.6	3.9	4.6
	Globulin	3.5	2.4	4.0	4.9	3.0	2.3	4.0	3.9	3.5	2.8	4.4	3.2
	Prothrombin	100		100	100	100		100	100	100	90	100	100
	Weltman test												
Urine and stool	Urine bilirubin												
	Urobilinogen	—	—	+	+	+	+	—	—	+	+	+	—
	Stercobilin												
	Fat in stool												
Surgery performed	Laparotomy	+	+	+	+	+	+	+	+	+	+	+	+
	Laparoscopy												
	Cholangiography												
	Liver biopsy	+	+	+	+	+	+	+	+	+	+	+	+

	Case no.	61	62	63	64	65	66	67	68	69	I	II	III	IV
Particulars from the anamnese	Age	17	68	61	44	38	48	46	43	52	39	66	53	66
	Sex	F	F	F	F	F	F	F	F	F	F	F	F	F
	Duration of disease	11	3	3	6	6	5	5	1	8	4	11	3	1½
	First symptom				J	P	P	J	J	J	J	P	P	J
	Appetite					G	G			7		Po.	G	Po.
	Wt. loss													
Clinical symptoms	Pruritus	+	+	+	+	+	+	+	+	—	+	+	+	
	Jaundice	+	+	+	+	+	+	+	+	+	+	+	+	+
	Abdominal pain			—	—	—	—	—	—	+	+	+	—	+
	Chills			—	—	—	—	—	—	—	—	—	—	
	Temperature			—	—	—	—	—	—	—	—	+	—	
	Diarrhea													
Physical examination														
Skin	Melanosis	+	+	+	+	+	+	—	+	—	—	+	—	
	Pyoderma	—	—	—	—	—	—	—	—	—	—	—	—	
	Xanthelasma	—	—	—	+	—	+	+	—	+	+	—	—	+
	Xanthoma	—	—	—	+	+	+	+	+	+	+	—	—	—
	Spiders	—	—	—	—	—	—	—	—	—	—	—	—	—
	Erythema palmaris	—	—	—	—	—	—	—	—	—	—	—	—	
Abdomen	Enlarged liver	8	8	6	+	8	10	10	+	+	+	4	4	10 cm.
	Enlarged spleen	+	+	—	+	—	+	—	+	+				
	Ascites													
Blood picture	Erythrocytes	3.6	4.4	4	3	2	3.7	4.5	3.6	no.	3.8	3.6	3.1	3.73
	Leucocytes	6,5	7,6	7,5	11	12	9	9,5	9,5	no.	43	3,4	2,7	6600
	Hemoglobin	11	13	12	69	22	71	13	11.5	no.	78	73		70%
	Color index	1.0	0.97	0.9	1.0	0.5	0.96	0.9	1.0	no.	1.0	1.0		0.93
	Sedimentation rate	19	43	42	86		18						42/80	130/140

Laboratory findings														
Liver function	Thymol turbidity	12	15	8							18.5	8.9	6	
	Thymol flocculation													+
	Gold flocculation													
	Cephalin flocculation							4+		16				
	Bromsulfalein	41	26	23		80	50			40				+
	Takata										+	+		+
	Galactose													
Blood chemistry	Total lipid	717	1735	915										
	Total cholesterine	196	521	429	1460	1115	1535	545	920	417	622			280
	Cholesterine esters				1305	972	1260	220	90	138	241			
	Phospholipids	259	875	319	2300	2240			1750					
	Serum bilirubin	25	12	8	6.6	13	20.4	5.2	9	4	6.1	3.9	10.9	2.8
	Serum iron													
	Serum copper													
	Alkaline phosphatase	29	52	138		27.5		23		35	20.9	19	8.9	38
	Total protein	7.7	8.5	7.7	8.6	5.3		7.6	8	8	7.6		8.4	
	Albumin	4.3	4.5	4.2	6.0	2.7		2.97	3.7	3.4				31.2%
	Globulin	3.4	4.0	3.5	2.6	2.6		4.68	4.3	4.7				68.8%
	Prothrombin	94	100	95										
	Weltman test													
Urine and stool	Urine bilirubin					+			+					
	Urobilinogen	+	+											
	Stercobilin													
	Fat in stool													
Surgery performed	Laparotomy	+	+	+	+	+	—	+	—	+	+	+	+	+
	Laparoscopy													
	Cholangiography										+	+	+	+
	Liver biopsy	+	+	+	+	+	—	+	+	+	+	+	+	+

(Case no. 1, 9, 12, 24, 25, 63). Case no. 7, 23, 26, 28, 61, 62, which are respectively 19, 10, 22, 16, 17, 68 years of age are the outstanding exceptions. The remaining cases comprising this group, are in their middle and late twenties (Case no. 2, 3, 5, 19, 20, 48), most of them male patients (Case no. 2, 3, 5, 19). As above noted, this disease can appear in a very early as well as in a very late period of life.

Sex:

Comparison of the sex of the 73 patients in this paper, results in a large number of females, namely 63, and a small group of males (10 patients). The ratio is approximately 6:1. Most of the female cases of this group were taken from the literature under the title of xanthomatous biliary cirrhosis [1, 2, 4, 8].

Duration:

One characteristic of this disease is the long duration. From our cases the range was from 1 to 34 years. However, the patients were not followed through in many cases, therefore this is not an exact account of the duration of the disease. Indeed, the onset cannot be determined in all cases, the best example being case no. 15. The history of this case indicated a continuous chronic disease of 34 years duration following the initial acute episode [12].

Pruritus:

The most striking first symptom of primary cholostatic cirrhosis is the stubborn pruritus or the painless jaundice. While final proof is lacking that the bile acids or their salts are responsible for pruritus, there can be little question that this symptom is due to a return of some constituent of bile into the blood, and hence that it may be regarded as a very characteristic manifestation of regurgitation or obstructive jaundice, with relatively normal hepatocellular function [12].

When external biliary drainage was used, for example in case no. 15, II, III, pruritus decreased considerably. Here one would have to assume that most of the bile salts being formed by the liver cell and excreted into the bile were returning promptly into the blood with an enterohepatic circulation, then, the decrease of pruritus, in the above metioned cases, may well have been due to interruption of the enterohepatic circulation of the bile salts.

Some authors [6], believe the pruritus and later skin efflorescence is due to the slowly developing hypersensitivity of the skin towards metabolic products.

First symptoms:

The first symptoms which appeared and usually led the patient to visit the doctor are variable, however, jaundice and pruritus were by far the most frequent.

Pruritus was the first symptom in 15 patients (Case no. 1, 4, 6, 8–10, 12, 19, 20, 27, 65, 66, II, III).

Jaundice appeared first in 11 patients (Case no. 2, 3, 17, 22, 24, 64, 67, 69, I).

Pain appeared as the first symptom in two patients (Case no. 7, 15). These patients usually complain of a feeling of increase of pressure beneath the right costal margin and not of colic pain [6].

Diarrhea was frequently mentioned in the case reports but only in three patients (Case no. 23, 25, 28) was it given as the first symptom of the disease.

Pruritus and jaundice appeared together in four patients (11, 13, 14, 26).

Appetite:

The appetite was good in seven patients (Case no. 2–6, 65, 66) and poor in five (Case no. 7, 13, 14, 18, II). However, the condition of the liver cannot always be held responsible for this symptom.

Wt. loss:

Wt. loss was prevalent in 17 patients including case no. 2–6, 65, 66, who all had good appetites. Perhaps this was due to faulty fat absorption [6].

Jaundice:

Jaundice appeared in all 73 cases. In 11 patients (Case no. 2, 3, 17, 21, 22, 24, 64, 67–69) it was responsible for their visit to the doctor.

The color of the skin is impure, that is, a brown-yellow hue. In one of our patients (Case no. II), the skin was brown, not icteric. This brown component is apparently due to development of melanosis (Case no. 2–7, 48–50, 52, 56–59, 61–63, 64–66, 68, II).

The cause of the melanosis is unknown. Considering the fact that this affection also appears in other pathological conditions and disturbances of fat metabolism, perhaps disturbance of fat resorption and also functional damage of the adrenal cortex can be considered as possible factors [6]. A skin biopsy was taken from case no. 5, 6 and

examined histologically. An accumulation of melanin in the basal layers of the epidermis with hyperkeratosis was seen [6].

From 47 patients, whose serum bilirubin concentration is known, 25 of them had values from 0.87–10 mg. % and the remaining 22 had concentrations from 10.16–34.8 mg. %.

The bilirubin values of patients, with jaundice and melanosis, was from 3.1–9 mg. % in 11 (Case no. 2, 4–6, 56–58, 63, 64, 68, II) and from 10.16–34.8 mg. % in the other 11 (Case no. 7, 49, 50, 52, 59, 61, 62, 65, 66).

Unfortunately, the intensity of jaundice in patients without melanosis was never described in any of the case reports.

Alkaline phosphatase:

The alkaline phosphatase, as compared to bilirubin concentrations, have been divided into three groups:

In group I, the alkaline phosphatase concentrations ranged from 7.21–19.7 and these patients had serum bilirubin values from 2.5–19.69 (Case no. 7, 9–12, 15, 17, 23, 26, 60, II, III).

In group II, alkaline phosphatase was from 20.91–52 and bilirubin from 0.87–22.64 (Case no. 1–6, 8, 13, 14, 19–22, 25, 48, 52, 56, 61, 62, 65, 67, 69, I, IV).

In group III, the range of alkaline phosphatase was from to 62–138 and bilirubin from 3.1–34.8 (Case no. 16, 24, 47, 49, 51, 53–55, 57–59, 63).

From the above data, it is seen, that no direct correlation between the alkaline phosphatase concentrations and serum bilirubin exists.

Furthermore, no relationship was found between the liver-function tests and alkaline-phosphatase values.

Abdominal pain:

Nine patients had abdominal pain (Case no. 2–5, 7, 15, 23, 28, 69), but as already mentioned, the complaint was of a feeling of increasing pressure below the right costal arch, not colic pain. However, in Case no. II, cramp-like pains of the upper abdomen spreading to the back and girdle-like in the abdomen were felt by the patient.

Chills:

Only four patients complained of chills (Case no. 4, 7, 15, 16), and eight had increased temperature readings (Case no. 4, 7, 10, 15–17, 23, II). These symptoms usually appeared together as seen in Case

no. 4, 7, 15, 16. Increased temperature usually does not appear at the beginning of the disease, as occurs in biliary cirrhosis after cholangitis, but during the disease; perhaps it is due to secondary infection from the long-standing cholostasis [6].

Pyoderma:

Pyoderma occurred in six cases (Case no. 3–7, 23). Scratching, to relieve pruritus, can result in secondary infection and often to efflorescence of the skin, especially pyoderma.

Xanthelasma and xanthomata:

Xanthelasma appeared in 35 cases, four of these were males (Case no. 3, 5, 18, 19).

Xanthomata, occurring as flat or slightly raised patches or nodular, from a pinhead to a bean in size, and of a yellow-orange color, occurred in two patients (Case no. 65, 68).

These affections appeared together in 26 cases (Case no. 3–6, 11, 16–20, 43–54, 64, 66, 67, 69). The total lipid concentration was above 2000 mg.% in Case no. 4, 6, 17–19, 20, 43–53, 64.

In Case no. 5, 11, 16, 66, 67, 69, total lipid concentrations could not be determined from the given data. However, the total choesterin values were very high, respectively, 1175, 1172, 1535 mg.% (Case no. 5, 16, 66).

It is noteworthy, that in case no. 21, 65, 68, the total lipid values were above 2000 mg.% but these patients had only xanthelasma. On the other hand, case no. 54 had a total lipid concentration of 1812 mg.% and she had both xanthelasma and xanthomata.

Ahrens and *Kunkel* [1], found that xanthelasma and xanthomata appeared together, in all patients with a total lipid concentration of 1800 mg.% or more. Only xanthelasma occurred when the total lipid concentration was 1300–1800 mg.%. If the total lipid values were below 1300 mg.%, then no xanthelasma or xanthomata was present.

It seems, from the above observations, that the appearance of xanthelasma and xanthomata cannot be explained on the basis of total lipid concentration.

It is known that in the course of the disease spontaneous variations of the lipid fraction can occur; however, for the development of xanthomata it is necessary that the total lipid concentration remain above the limiting value for a definite time. Therefore, it is possible

that xanthomata do not develop in certain cases because the concentration of total lipids above the limiting value, did not remain stationary for a long enough time. The appearance of xanthelasma or xanthomata depends, perhaps, exclusively on whether or not, in the course of the disease, a disturbance of fat metabolism has occurred [6].

Spiders:

The appearance of spiders, which are much more often encountered on the face, back of the neck, shoulders, arms, hands or upper chest, were present in five cases (Case no. 5, 6, 18, 49, 50).

Erythema palmaris:

Flushing of the thenar and hypothenar eminences (liver palm) was noted in seven cases (3, 4, 50–52, 56, 62).

Enlargement of the liver:

With the exception of two patients (Case no. 8, 9) the liver was found enlarged in all cases, the maximum reaching to 17 cm. below the costal margin.

The color of the liver was yellow-green to dark green with a smooth to finely granulated surface. A slightly nodular liver was described in case no. 20, 27, respectively nine and three years after the onset of symptoms, the liver was described as moderately enlarged, granular, and fibriotic, and interpreted grossly as portal cirrhosis.

From our four patients, Case no. III, had a large, dark-red liver with a finely granulated surface, not green as is usually seen in biliary cirrhosis and in practically all cases in this paper. A hobnail nodular appearance (Laennec cirrhosis) was not observed in any case.

A hepatosplenomegaly was found present in 35 patients (Case no. 2–7, 11, 14–18, 20–23, 25–28, 47–50, 52, 56, 59–62, 64, 66, 68, 69, II).

An enlarged liver alone was found in 35 cases (Case no. 10–13, 19, 24, 29–46, 51, 53–55, 57, 63, 65, 67, I, III, IV).

Ascites:

Ascites was described in four cases (Case no. 16, 18, 22, III), respectively, 10, 6, 4, $1^1/_2$ years, perhaps even longer, after the onset of symptoms. Portal hypertension, during this disease, was encountered in only one patent (Case no. III), 3 years after diagnosis.

Blood picture:

The blood picture shows erythrocyte counts of either normal in 23 patients, or below normal values seen in 21 cases. *Ahrens* [1], accounts for the development of anemia in primary cholostatic cirrhosis as due to the long duration of fat metabolism disturbance and the insoluble binding of iron and fatty acids in the intestine.

The leucocyte counts were normal in 18, increased above the normal in 21 and below the normal in three patients. The leucocytosis is due, in certain cases, perhaps to secondary infection resulting from the long-standing cholostasis.

When one considers the normal range of hemoglobin values to be from 12–16 gm. %, then we see that 25 patients had a normal and 18 a below the normal hemoglobin value.

Sedimentation rate:

With few exceptions (Case no. 2, 61, 66), the sedimentation rate was very high in all cases where it was given. In case no. 3, 8, 10, it was extremely high, respectively, 110/130, 124/140, and 141/145.

Liver functions:

We find 38 patients with a pathological Thymol turbidity, nine with pathological thymol flocculation and 15 cases that show pathological cephalin tests.

In normal subjects, bromsulfalein is completely cleared from the serum in 30–45 minutes. There was retention of the dye in 22 patients, indicating the presence of hepatic insufficiency.

Total lipoids:

An analysis of the serum showed that total lipids were increased above the normal value, in 36 cases, the maximum reaching to 6475 mg. % (Case no. 20).

Total cholesterin:

Normally, the total cholesterin concentration corresponds to 150 to 260 mg. %. It was found normal in six patients (Case no. 2, 7, 11, 29, 61, 67), and increased above the normal in 61 cases.

Cholesterin esters:

We will consider the cholesterin esters normal, when they correspond to 70–75 % of the total cholesterin concentration, that is, the normal values would range from 105–195 mg. %.

Five cases (Case no. 18, 19, 21, 22, 69), fall within the normal range, ten are above normal (Case no. 8–10, 16, 20, 64–67, I), and three patients had a below the normal concentration (Case no. 25, 26, 28).

Phospholipids:

Two cases (Case no. 29, 61), had normal values, 43 above normal (Case no. 2–8, 18–20, 30–60, 62–65, 68), and case no. 16 had an extremely low value of 80 mg. %. We consider the normal value as 150 to 260 mg. %.

Serum iron:

The serum iron concentration was determined in 11 cases (Case no. 2–12). If we take 90–150 gamma % as normal, we find that in five cases (Case no. 2, 4, 5, 6, 8), the concentration is above normal while in four (Case no. 3, 9. 10, 12), the value is normal and in two the value is below normal (Case no. 7, 11).

Serum copper:

The serum copper was increased above the normal value in all the cases (Case no. 8–12), in which it was given.

It is generally recognized that for the proper utilization of iron, small quantities of copper are needed. Without the copper, the iron is assimilated but not converted into hemoglobin; such a conversion does take place in the presence of copper *(Elvehjem)*. Perhaps this can be considered as a factor producing anemia in this disease.

Serum proteins:

The total protein concentrations were normal in 15 patients, while two had below normal values (Case no. 11, 65). Above normal values were found in 27 patients.

The serum albumin remained within the normal limits in most cases (Case no. 2–9, 13–17, 20–22, 26, 47–49, 51–63, 68), below normal in case no. 3, 10–12, 18, 19, 23, 26, 55, 65, 67, 69, and above the normal concentrations in case no. 50, 64.

Serum globulins were normal in six patients (Case no. 14, 48, 53, 58, 64, 65), below in case no. 26, 50, 64, and increased above the normal value in 39 cases, as is expected, in this disease.

From the electrophoretic separation of serum proteins, some authors [10], found elevation of the beta globulins in every case in which it was measured, forming a pattern similar to that described by *Gray*, *Barrom*, *Kunkel* and *Ahrens*.

Prothrombin:

The prothrombin time was normal in 33 patients and decreased in two (Case no. 10, 11). It is now recognized that the prothrombin time should be determined prior to every operation in which it is theoretically possible that the liver may be disturbed, or in which there may be an absolute or relative deficiency of vitamin K or a disturbance of its utilization.

Findings at operation:

An exploratory laparotomy is usually performed to relieve the patient of an extrahepatic obstruction. Unfortunately, not complete data was given for all patients in the case reports. However, we found from 69 cases in the literature and four cases (Case no. I, II, III, IV), which we observed, that 45 had laparotomies.

Enlarged lymph glands, found near the gallbladder and extrahepatic ducts, seems to be a constant finding in primary cholostatic cirrhosis. This was reported in nine cases (Case no. 2, 4–7, 9, 10, 20, 27), in the literature and in two of our cases (Case no. I, II).

Sometimes, the enlarged lymph glands were thought to be the cause of obstruction. However, no improvement of the patients condition, was reported after their removal in any of the cases, presented in this paper.

A laparoscopy was done on six cases (Case no. 8–11, 13, II). This method is not valuable because it is not possible, from the aspect of the liver surface, to differentiate between intra- and extrahepatic obstruction.

A cholangiography is irreplacable as a diagnostic help, for the diagnosis of primary cholostatic cirrhosis because it is the only method to give sufficient evidence of normal extrahepatic bile ducts. It was performed on only 11 patients (Case no. 2–7, 13, I, II, III, IV) from the 73 reported cases.

When a suspicion exists, that a patient has primary cholostatic cirrhosis, we advise an exploratory laparotomy followed by a cholangiography.

If a laparotomy is performed without cholangiography, the patient usually appears in the operating room again for a second laparotomy (Case no. 20, I).

Therefore, it cannot be emphasized enough, that a laparotomy followed by a *cholangiography*, is absolutely necessary for the surgeon

do diagnose, with certainty, that no obstruction of the extrahepatic duct exists.

Liver biopsy:

A liver biopsy was taken from 50 patients of the reported 73. The most significant lesion was found in the smaller bile ducts (junction ducts or canals of Hering), and terminal bile ducts (interlobular bile ducts or cholangioles), at the periphery of the lobules.

The portal areas are larger, broader and longer than usual and fused with one another to form rings of perilobular fibrosis (Case no. II, see *operation*).

There is an increase of fibrous connective tissue in all preparations we have seen and the amount and extension is very variable, from one case to another.

The larger bile ducts are patent and empty. The small interlobular bile ducts are very difficult to find and in many of the portal areas completely missing. The junction ducts (canals of Hering), are often dilated and filled with bile thrombi and at times collapsed and empty.

The lobular pattern of the liver is not always well preserved, sometimes, large bile casts are fairly numerous within the lobules. These bile casts can distend the canaliculi and damage the bordering liver cells.

A distinguished feature is the almost constant preservation of the liver parenchyme, with no evidence of fatty or hyaline degeneration or distortion of the cord pattern. Minor to marked changes in the parenchyme are limited to the periphery of the lobule immediately adjacent to the pericholangitis and to the areas of proliferation of the bile canaliiculi and fibrosis. In these areas there are sometimes large hepatic cells with granulated cytoplasm, multiple nuclei and degenerative features (see preparation Case no. I, II).

The one fundamental histological finding in primary cholostatic cirrhosis, is the chronic inflammatory reaction in the interstitial portal areas (see preparations, Case no. I, II, III, IV). In the later stages of the disease, encroachment of connective tissue into the liver lobule and formation of pseudo-lobules results (see preparations, Case no. II). During the terminal stage of the disease, signs of a diffuse cirrhosis with extensive periportal and intralobular connective tissue infiltration predominates (see preparation, Case no. I, II, III, IV).

The histological findings of cases with xanthomatous changes of the skin compared to those with none, show no striking differences.

Only the total lipid concentration of the blood serum separate the two groups, and offer us an explanation for the development of xanthomatas and xanthelasmas.

Furthermore, if the disease is of sufficient chronicity, extensive fibrosis, fragmentation and disappearance and regeneration of the lobules without active inflammatory features apparently may be found [10]. Then the histologic diagnosis may be difficult, and it may be interpreted as portal cirrhosis, as was done in case no. 20 of this series.

Etiology:

The etiology of this disease is unknown. From the present day literature, it is difficult to gain any vital etiologic item of information.

Foremost, the question of any connection with virus hepatitis, presents itself. However, in only a very few cases, was a virus infection of the liver found as a preceding disease.

In the past years, the increased number of the so-called cholostatic form of hepatitis has been observed. This form presents itself, the same as in primary cholostatic cirrhosis, under the picture of an obstruction icterus with high alkaline phosphatase, long intact liver functions and prolonged bromsulfalein excretion time. It constitutes, as it were, the acute course of that, which as a chronic disease, represents primary cholostatic cirrhosis.

However, enticing the supposition may be, that primary cholostatic cirrhosis represents the final stage of cholostatic hepatitis, nevertheless, any observation is lacking which would prove such development.

Acute intrahepatic cholostasis, of similar clinical pictures, has been observed after treatment with testosterone and especially chlorpromazine. In regards to primary cholostatic cirrhosis, however, any indication is lacking, that chronic exposition with such medicaments may play a roll in etiology.

Summary

(1) We have presented a report of 73 proven cases, four of which were under our observation. The particulars of the clinical picture and differential diagnosis were considered in our discussion.

(2) Synonyms for primary cholostatic cirrhosis are: pericholangiolitic biliary cirrhosis, chronic intrahepatic obliterating cholangitis, non-obstructive cholangitic biliary cirrhosis, intrahepatic cholangitic

biliary cirrhosis, Hanot's biliary cirrhosis, xanthomatous biliary cirrhosis, and primary biliary cirrhosis.

(3) A thorough description of the pathological histology features of this disease is presented. The one fundamental histological finding in primary cholostatic cirrhosis is the chronic inflammatory reaction in the interstitial portal areas beginning as pericholangiolitis and spreading gradually to the peripheral fields of the adjacent lobules.

(4) The impossibility, in many cases to make a clinical diagnosis of this disease, and the value of cholangiography to establish the final diagnosis was discussed.

(5) The most important criteria for the diagnosis:

I. *Clinical:* (1) Jaundice-pruritus; (2) Hepatosplenomegaly; (3) Skin manifestations (optional), (a) Xanthelasma, (b) Xanthoma.

II. *Biochemical:* (1) Hypercholesteremia; (2) Hyperlipemia with clear serum; (3) Alkaline phosphatase activity is increased; (4) Hyperbilirubinemia; (5) Liver function tests may be normal or pathological.

III. *Morphological:* (1) Cirrhosis or fibrosis of the liver; (2) Pericholangitis; or pericholangiolitis; (3) Bile stasis (cholostasis).

Zusammenfassung

73 Fälle (davon 4 eigene) von primärer cholestatischer Lebercirrhose werden mitgeteilt und das Krankheitsbild und die Differentialdiagnose besprochen. Diskussion der Nomenklatur.

Die pathologische Anatomie wird beschrieben; charakteristisch ist eine pericholangiolitisch beginnende chronische entzündliche Reaktion im periportalen Bindegewebe mit allmählichem Übergreifen des Prozesses in die nächstliegenden Läppchen.

Es wird darauf hingewiesen, daß klinisch die Diagnose in manchen Fällen nicht gestellt werden kann; der diagnostische Wert der Cholangiographie wird diskutiert.

Die wichtigsten diagnostischen Kriterien sind:

1. Klinisch: Ikterus mit Pruritus, Hepato-Splenomegalie, Hautveränderungen, Xanthelasma, Xanthom.

2. Biochemisch: Hypercholesterinämie, Hyperlipämie mit klarem Serum, erhöhte alkalische Phosphatasewerte, normale oder pathologische Leberfunktionsteste.

3. Morphologisch: Cirrhose oder Fibrose der Leber, Pericholangitis oder Pericholangiolitis, Cholostase.

Résumé

1° Compte-rendu de 73 observations de cirrhose cholostatique primitive certaine, dont 4 personnelles; description du tableau clinique et discussion du diagnostic différentiel.

2° De nombreux synonymes ont été proposés pour la cirrhose cholostatique primitive.

3° Description des particularités histo-pathologiques de cette affection. L'aspect caractéristique consiste en une réaction chronique inflammatoire du territoire portal interstitiel, commençant comme une péricholangite et s'étendant progressivement jusqu'à la périphérie des lobules adjacents.

4° Devant l'impossibilité fréquente de poser ce diagnostic à l'aide de la seule clinique, c'est la cholangiographie qui permettra de trancher.

5° Le diagnostic se base sur les critères essentiels suivants:

a) *Cliniques:* ictère prurigineux; hépatosplénomégalie; manifestations cutanées (facultatives); xanthelasma et xanthome.

b) *Biochimiques:* hypercholestérolémie; hyperlipémie sans sérum lactescent; augmentation des phosphatases alcalines: hyperbilirubinémie; tests fonctionnels hépatiques soit normaux, soit perturbés.

c) *Morphologiques:* cirrhose ou fibrose hépatiques; péricholangite ou péricholangiolite; stase biliaire (cholostase).

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